

DISSERTATION ON

**EVALUATION OF CLINICORADIOLOGICAL
PULMONARY MANIFESTATIONS IN TYPE 2
DIABETES MELLITUS AND CORRELATION
BETWEEN PULMONARY FUNCTION TEST AND
GLYCEMIC CONTROL.**

Dissertation submitted to the

**Dr.M.G.R.MEDICALUNIVERSITY,
TAMILNADU.**

*In partial fulfillment of the requirements
For the degree of Doctor of Medicine in*

**TUBERCULOSIS AND RESPIRATORY MEDICINE
BRANCH-XVII
INSTITUTE OF THORACIC MEDICINE**



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Rajiv Gandhi Government General Hospital
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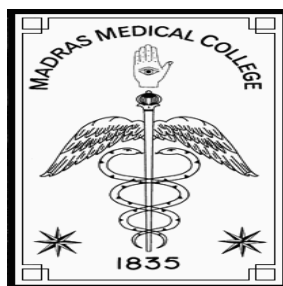
BONAFIDE CERTIFICATE

Certified that this dissertation is the bonafide work of **Dr.SURYA.B.PILLAI** on “**EVALUATION OF CLINIC ORADIOLOGICAL PULMONARY MANIFESTATIONS IN TYPE 2 DIABETES MELLITUS AND CORRELATION BETWEEN PULMONARY FUNCTION TEST AND GLYCEMIC CONTROL**” during her MD (TB & RESPIRATORY MEDICINE) course from April 2010 to April 2013 at INSTITUTE OF THORACIC MEDICINE AND RAJIV GANDHI GOVERNMENT GENERAL HOSPITAL-MADRAS MEDICAL COLLEGE, CHENNAI.

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DECLARATION BY THE SCHOLAR

I hereby declare that the dissertation entitled **“EVALUATION OF CLINIC ORADIOLOGICAL PULMONARY MANIFESTATIONS IN TYPE 2 DIABETES MELLITUS AND CORRELATION BETWEEN PULMONARY FUNCTION TEST AND GLYCEMIC CONTROL”** submitted for the degree of Doctor of medicine in M.D.DEGREE EXAMINATION Branch XVII TB&RESPIRATORY MEDICINE is my original work and the dissertation has not formed the basis for the award of any degree, diploma, associate ship, fellowship or similar other titles. It had not been submitted to any other university or institution for the award of any degree or diploma.

Place:Chennai
Date:

Signature of the scholar

Name:Dr.SURYA.B.PILLAI

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EVALUATION OF CLINICORADIOLOGICAL PULMONARY MANIFESTATIONS IN TYPE 2 DIABETES MELLITUS AND CORRELATION BETWEEN PULMONARY FUNCTION TEST AND GLYCEMIC CONTROL.

BACKGROUND:

Diabetes mellitus is increasing in global prevalence with India having more than 50 million diabetic population. Diabetes mellitus causes the lungs to deteriorate quicker than they do normally with age. Impaired immune response in diabetes can cause recurrent infections. Higher blood sugar results in diabetic microangiopathy and non enzymatic glycosylation of tissues causing alveolar basement membrane thickening, deposition in collagen of chest wall and bronchial tree causing muscle weakness. This results in decreased gas transfer, diminished lung function and air flow limitation. There are very few data regarding pulmonary function in type 2 diabetes especially in Indian population.

AIM OF STUDY

- 1) Correlation between pulmonary function in diabetic patients based on PFT values and glycemic control
- 2) Various clinical and radiological pulmonary manifestations in diabetes mellitus

MATERIALS & METHODS:

Prospective study of 150 patients was carried out in Thoracic medicine department, Madras Medical College over 8 months. All patients with age more than 30 years with proven Type II diabetes mellitus with or without respiratory symptoms/signs were included. Diabetic status assessed by FBS, PPBS, HbA1C. Chest X ray, Sputum AFB, gram stain, C&S, fungal smear and culture, Mantoux were done. PFT was done in patients and control population. All findings correlated with duration of diabetes and glycemic control.

RESULTS

Of the 150 patients in the study group 91 were males and 59 were females. 60% of the study group were symptomatic, of which 37.3% were males & 22.7% were females. Of the symptomatics (n=90), 50% had pulmonary tuberculosis, 33.3% had other bacterial and fungal infections, 16.6% had no active infection, 60% Mantoux negative & 40% were Mantoux positive. Of the pulmonary TB patients 71.1% were sputum positive & 28.8% were sputum negative. 65.6% of sputum positive were Mantoux positive. Radiologically most common finding in pulmonary TB was lower lung field TB. Klebsiella pneumonia was the most common bacterial infection other than TB. Pulmonary function tests were done in 60 asymptomatics & 15 symptomatics without active infection and 75 age and sex matched control population. FEV1 and FVC showed statistically significant reduction in diabetics compared to non diabetic controls. Decrease in FEV1 and FVC correlated with duration of diabetes, but not with HbA1C levels.

Key words: diabetes mellitus, non enzymatic glycosylation, FEV1, FVC, HbA1C

INTRODUCTION

Diabetes mellitus is a disease that is increasing in epidemic proportion in asian countries with India having more than 50 million diabetic population. It is estimated to affect 336 million people world wide by 2050 with 7 million new diabetic cases. Diabetes mellitus is associated with widespread metabolic, hormonal and micro vascular abnormalities as well as disturbance of function of organ systems.

Lung can be involved in the pathogenesis of diabetes and can be considered as another end organ adversely affected by diabetes. It can cause premature aging of lungs. Higher blood sugar level result in

Diabetic microangiopathy and non enzymatic glycosylation of tissue proteins causing alveolar epithelium basement membrane thickening.

Glycosylation can also cause deposition in collagen of chest wall and bronchial tree causing muscle weakness. This result in decrease gas transfer, diminished lung function and air flow limitation. Diabetes can also lead to autonomic neuropathy. Impaired immune response in diabetes can cause recurrent bacterial pneumonia, fungal infections and Tuberculosis.

Diabetes is an independent risk factor for tuberculosis both drug sensitive and multidrug resistant.

There are many studies showing pulmonary function in type 1 diabetes mellitus, but very few data regarding pulmonary function in type 2 diabetes especially in Indian population.

AIM OF STUDY

1. To study the various clinical and radiological pulmonary manifestations in diabetes mellitus.
2. To study the correlation between pulmonary function in diabetic patients based on PFT values and glycemic control assessed by FBS , PPBS, HbA1C.

REVIEW OF LITERATURE

Diabetes mellitus is a group of metabolic diseases characterised by hyperglycemia resulting from defects in insulin secretion, insulin action or both. Chronic hyperglycemia in long standing diabetes is associated with long term damage and dysfunction in various organ systems of the body.

Two types of diabetes are type1 diabetes mellitus and type 2 diabetes mellitus.

Type1 diabetes mellitus:

It presents most often in younger patients. It is less common than Type2 diabetes mellitus. It is caused by absolute deficiency of insulin secretion due to autoimmune pathologic process in pancreatic islets against islet cell cytoplasmic proteins.

Type2 diabetes mellitus :

Most common type, adult onset disease caused by insulin resistance and inadequate compensatory insulin response. In type 2 diabetes mellitus degree of hyperglycemia is sufficient to cause pathologic and functional changes in target tissues and may be present for a long period of time without clinical symptoms before diabetes is

detected. Major morbidities in type 2 diabetes are due to its microangiopathic complications.

There are many studies showing that lung is a target organ in diabetes mellitus and poor glycemic control is a strong determinant of reduced pulmonary function in type2 diabetes.

Pulmonary complications in diabetes mellitus

- 1) pulmonary infections
- 2) Pulmonary function abnormalities
- 3) Abnormal basal airway tone
- 4) Unexplained dyspnoea due to phrenic neuropathy causing diaphragmatic palsy
- 5) Obstructive sleep apnoea and other patterns of disordered breathing during sleep
- 6) Pulmonary hypertension
- 7) In diabetic ketoacidosis increased predisposition to ARDS
- 8) New born babies of diabetic mothers –neonatal respiratory distress syndrome.

PULMONARY INFECTIONS IN DIABETES

Chronic hyperglycemia in diabetes can lead to alterations in host defence mechanisms and local lung defence mechanism by altering function of respiratory epithelium and ciliary motility.

Characteristics of pulmonary infection in diabetes

Longer duration of infections

Recurrent bacterial pneumonias

Severity of clinical presentation

Severe complications

Increased morbidity & mortality

Pathogenesis of pulmonary infections in diabetes

Hyperglycemia in diabetes impairs function of neutrophils and

monocytes. It affects *chemotaxis

 *adherence

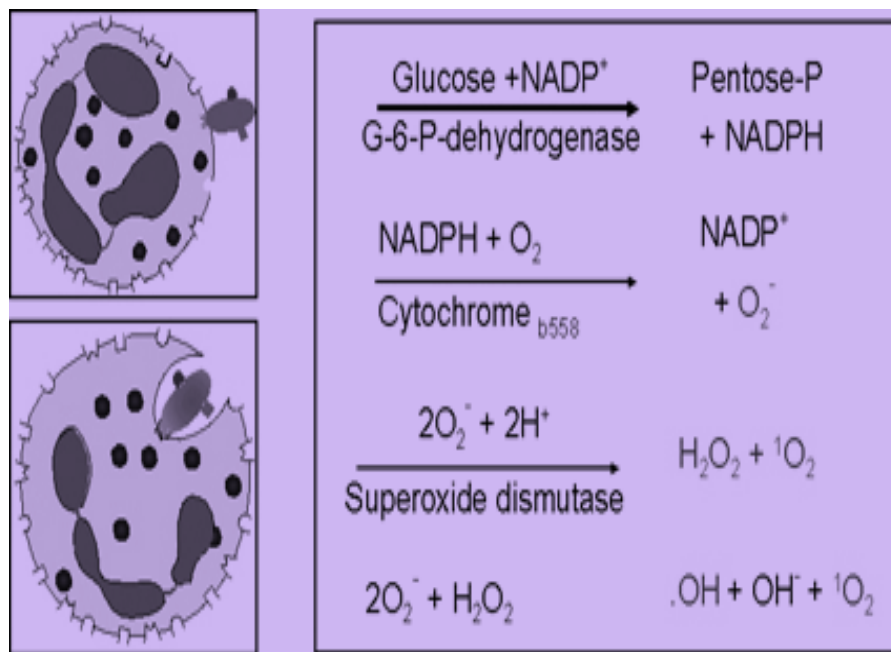
 *phagocytosis

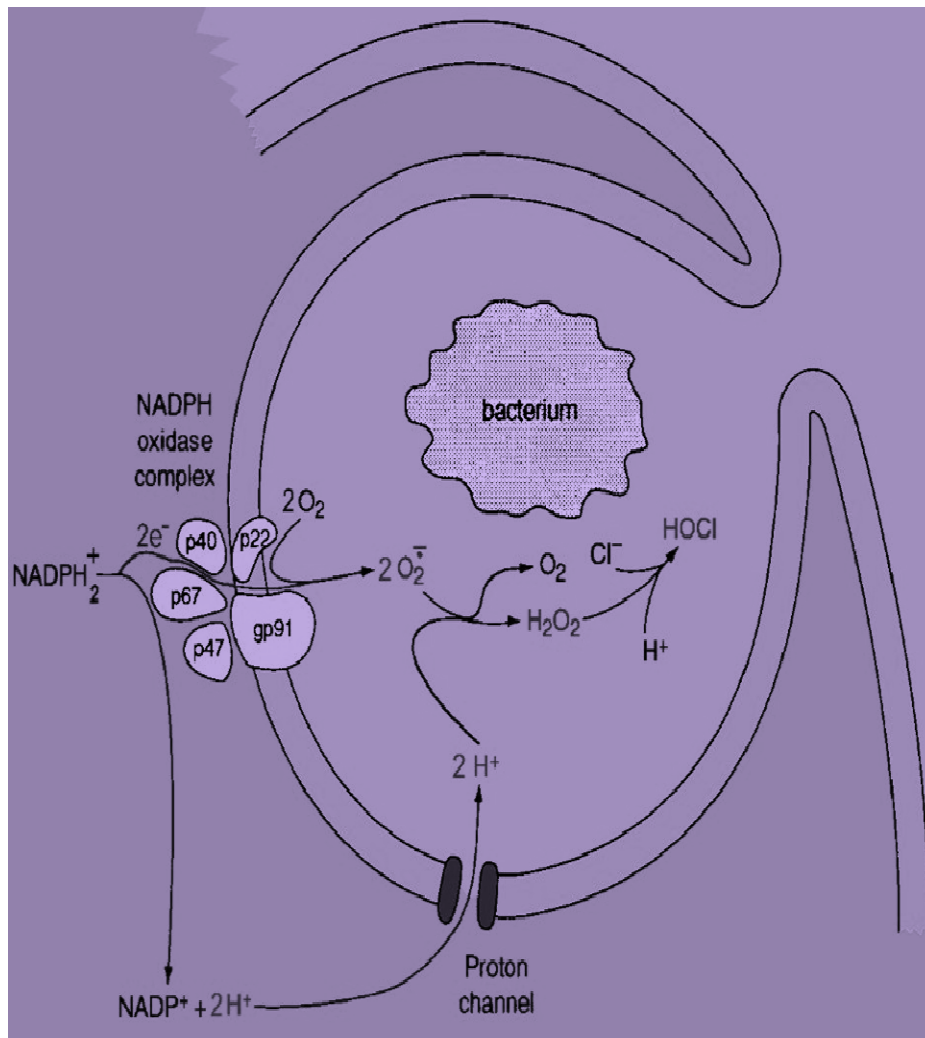
 *ability of intracellular microbial killing.

Levels of serum complement and T helper lymphocytes are reduced in diabetes, interfering with immune defense mechanisms.

Due to alteration in immune response, movement of phagocytic cells to the site of infection is impaired. Intracellular killing of microbes usually occurs by respiratory burst mechanism, by the production of superoxides and hydrogen peroxide free radicals. Free radical production depends on nicotinamide adenine dinucleotide phosphate or NADPH.

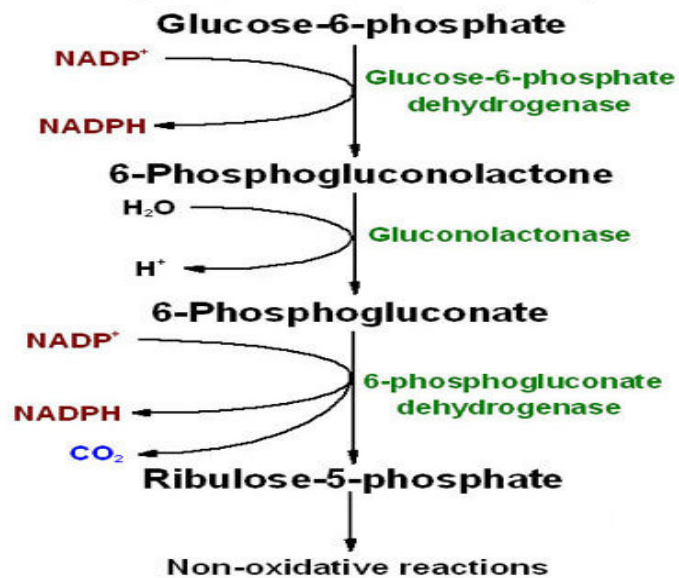
Free Radical production by Respiratory Burst Mechanism





Respiratory burst mechanism

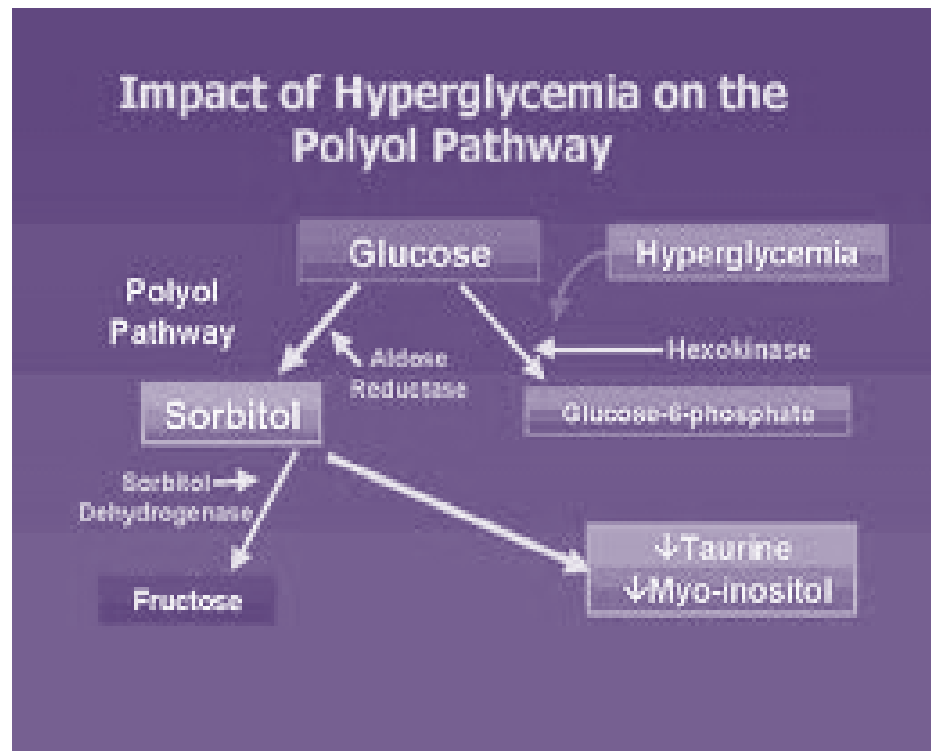
NADPH is normally generated by hexose monophosphate shunt pathway



In diabetes, hyperglycemia lead to more glucose entering the cells which is metabolised by the polyol pathway. This pathway converts glucose to sorbitol by aldose reductase enzyme, which requires NADPH.

As a result of this two major consequences occur.

- 1) Elevated sorbitol levels can lead to complications in diabetes.
- 2) Competition for NADPH results in decreased production of free radicals by oxidative burst and reduces intracellular killing of microbes.



Chronic hyperglycemia also lead to alteration in

- *Function of capillary endothelium

- *Rigidity of RBCs

- *Changes in oxygen dissociation curve.

So it affects microcirculation and can lead to greater risk of infections

in long standing diabetes reduced oxygen supply lead to infection by

anaerobic organisms.

Diabetic gastroparesis can increase the risk of aspiration in diabetes. Abnormality in ciliary motility also adds to impaired clearance mechanisms and predispose to infections. In response to infection and cytokine release, insulin resistance occurs in peripheral tissues and results in blood sugar elevation.

Common respiratory infections in diabetes mellitus

Staphylococcus aureus infections and gram negative bacterial infections are seen with increased frequency in diabetes. Streptococcus pneumonia, Legionella pneumophila, Viral infections are associated with increased morbidity in diabetes.

Staphylococcus aureus infections

Due to increased nasal carriage of staphylococcus aureus in uncontrolled diabetics, they are more prone for staphylococcal pneumonia and its complications. This nasal carriage is influenced by degree of glycemic control.

Gram negative aerobic infections

In diabetics gram negative aerobes have an increased adherence and thus increased rate of colonisation in upper airways. This leads to increased predisposition to infection in them.

Anaerobic pulmonary infections

Anaerobic infections are more common in diabetics due to

1. altered clearance mechanisms
2. altered cough mechanism
3. disorders of oesophagus
4. hypoglycemic seizures causing depressed mental status
5. changes in microcirculation causing decreased oxygen supply

predisposing to anaerobic infections

Streptococcus pneumonia

Group B streptococcus pneumonia is the most severe microorganism causing infection in diabetes. It is a risk factor for the development of bacteremia in pneumococcal pneumonia resulting in mortality. So immunization against pneumococci is advised in diabetes.

Viral pneumonia

Increased predisposition for influenza virus pneumonia is seen in diabetes, associated with increased morbidity and mortality. Influenza epidemics are associated with increased rate of pneumonia in diabetics, increased chance of diabetic ketoacidosis and increased mortality, so prophylactic influenza vaccine is advised in diabetics.

Fungal pneumonia

Fungal pneumonias are more common in diabetics. Most common fungal infection is aspergillus infections.

Nosocomial pneumonia

Usually nosocomial pneumonia in diabetics are caused by Staphylococcus aureus and gram negative aerobes. Klebsiella pneumonia and Staphylococcal infections are associated with more severe clinical course.

Complications of pneumonia in diabetics.

Non resolving pneumonia

Recurrent pneumonia

Parapneumonic effusion

Empyema

Bacteremia

Tuberculosis in diabetics

Causes for increased predisposition for tuberculosis in diabetics

1. Association between HLA DRB1 and HLA DQB1 and pulmonary tuberculosis complicated with diabetes. HLA DRB1 increases susceptibility to pulmonary TB in diabetes .HLA DQB1 is protective for pulmonary TB in diabetes.
2. neutrophilic dysfunction
3. impaired cytokine production
4. decreased interferon α production capacity
5. decreased production of Interleukin 1β and tumor necrosis factor α
6. non enzymatic glycosylation of tissue proteins causing alterations in connective tissue and increased susceptibility to TB.

Clinical presentation of pulmonary TB in diabetes

Tuberculosis in diabetes is usually due to reactivation of old focus of infection. It occurs as more advanced disease with lower lung field involvement and consolidatory changes than usual.

Cavitary lesions are more common. Cavities are large about 2-4 cm in an area of consolidation. American thoracic society and centre for disease control considers diabetes as a special situation and prescribe chemoprophylaxis with isoniazid in diabetics with positive mantoux test.

Patients with active tuberculosis are at more risk of developing diabetes mellitus. Possible explanations for these are

1. In active pulmonary TB-immuno reactive insulin, C-peptide, glucose levels before and after glucagon stimulation shows absolute insulin deficiency and more frequent development of severe diabetes
2. Functional disorders of the insular system of pancreas more evident in middle aged and elderly with pulmonary tuberculosis.

3. Tuberculous pancreatitis-a chronic pancreatitis of tubercular origin may be revealed only with the development of diabetes mellitus.

Consequences of co-existing tuberculosis and diabetes

1. Type 2 diabetes involving high blood sugar levels is associated with altered immune response to tuberculosis.
2. These patients take longer time to respond to anti TB treatment.
3. Patients with active TB and Diabetes are more likely to develop multidrug resistant tuberculosis.
4. Active tuberculosis patients with diabetes should be treated with Insulin

Problems in treatment of co-existing tuberculosis and diabetes are

1. Anti tuberculosis drugs affect the beta cell function of pancreas and unmask the diabetic status of the patients.
2. Rifampicin is a potent hepatic enzyme inducing agent that accelerates the metabolism of oral hypoglycemic agents. This causes early hyperglycemia and increases insulin requirement in tuberculosis patients.

3. Biguanides (Metformin) has anorectic action, causes malabsorption. This causes weight loss, exaggerating the weight loss already caused by TB.
4. Sulfonyl ureas are also not indicated in patients taking ATT.
5. Indication for withholding OHA in diabetes patients with TB -
Marked weight loss
 - Increasing age
 - Longer duration of diabetes
 - Higher insulin and caloric needs in TB.
6. Use of insulin jet injector in diabetes increases the risk of Mycobacterium Chelonae infection.

Pulmonary function abnormalities in diabetes

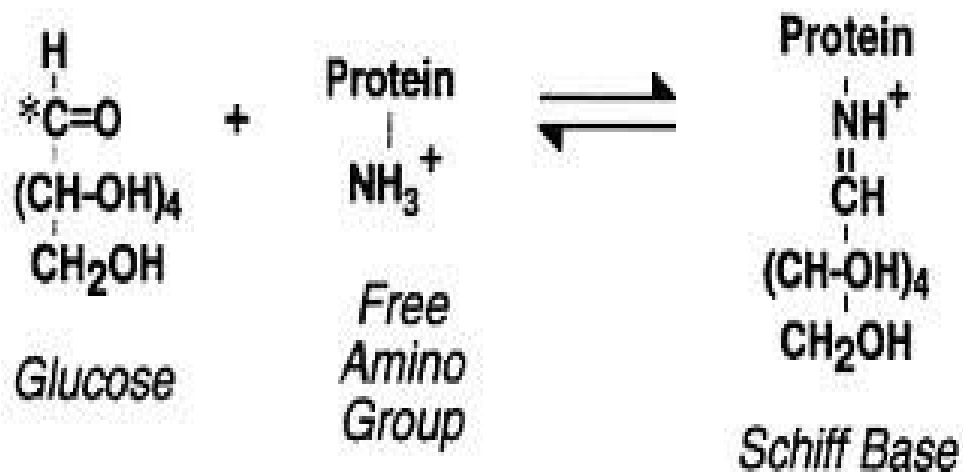
1. Decreased vital capacity
2. Decreased total lung capacity.
3. Decreased pulmonary elastic recoil.
4. Impaired alveolar gas exchange
5. Decreased DLCO
6. Decreased maximal oxygen uptake
7. Decreased inspiratory muscle strength
8. Peripheral airway dysfunction
9. Abnormal basal airway tone due to alteration in vagal pathway caused by diabetic autonomic neuropathy. This leads to decreased bronchial reactivity and reduced bronchodilation.

Pathogenesis of pulmonary function abnormalities in diabetes

Development of lung abnormalities in diabetes are due to alterations in lung connective tissue at biochemical level. All these changes are brought about by non enzymatic glycosylation of tissue proteins and pulmonary microangiopathy. In healthy non smokers usual rate of decline in FEV1 is 25-30 ml/year. In long standing diabetes decline can be up to 71 ml/year.

Non enzymatic glycosylation of proteins

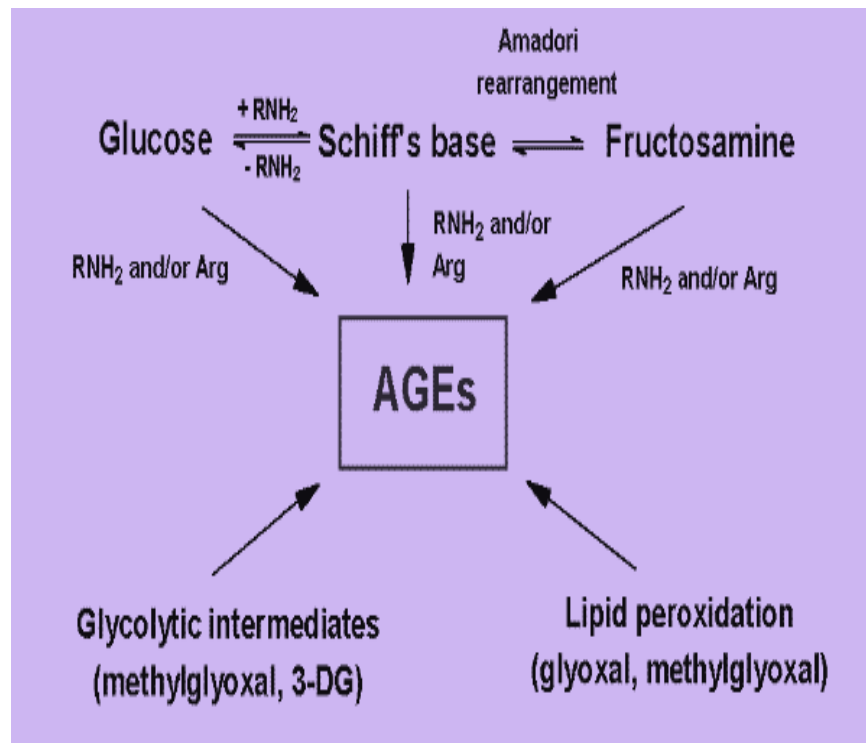
Enzymatic addition of any sugar to a protein is called glycosylation and non enzymatic process is called glycation. Hyperglycemia leads to glycation of proteins in the body. Glucose forms Schiff base with N- terminal amino group of proteins. Glucose molecule first attaches to N-terminal amino group by an aldimine linkage. Once attached glucose is not removed from haemoglobin in RBC. They remain throughout the life span of RBC, 120 days.



NON ENZYMATIC GLYCOSYLATION

Glycation also occurs in albumin, collagen etc. Glycated tissue proteins such as collagen are called advanced glycation end products. Glycation of matrix proteins once occurred is completely irreversible. They are further condensed to heterocyclic imidazole derivatives. Accumulation of advanced glycation end products lead to cross linking of matrix proteins with altered function. Rate of formation of advanced glycation end products is proportional to square of glucose concentration.

Normal elastance and compliance of lung require all connective tissue elements in harmony and proper spatial orientation. Strength and stability of connective tissue is provided by cross link formation of both collagen and elastin components.



Pulmonary microangiopathy is evidenced by thickening of alveolar capillary and pulmonary arteriolar walls and decreased lung capillary blood volume in patients with diabetes mellitus. Initial lesion in diabetic microangiopathy is thickening of basal lamina.

Structural changes in lung parenchyma in diabetes

1. Narrowing of alveolar space
2. Flattening of alveolar epithelium
3. Expansion of interstitium
4. Involvement of pulmonary vessel
5. Involvement of basement membrane of alveolar epithelium, bronchial epithelium and pulmonary capillaries.

Histological changes occurring in the lungs are of two types

- Increased amounts of collagen and elastin causing thickening of basement membrane of alveoli and pulmonary alveolar wall thickening.
- Due to fibroblast proliferation and deposition in capillary endothelium , thickening of basement membrane of capillaries.

So impairment in alveolar capillary membrane occurs which causes increase in distance and time of gas exchange between alveoli and RBC in pulmonary capillaries. Barrier thickening lead to decreased oxygen saturation in erythrocytes.

There are several studies using electron microscope that shows thickening of basal lamina is of same magnitude in lung and kidney. In early stages of diabetes this lung damage may be subclinical.

Diabetes can affect the strength and endurance of muscles of respiration especially diaphragm. It also causes deleterious effects in collagen structure of lung parenchyma and chest wall cartilage. These changes limit motility of chest wall.

Peripheral airway dysfunction can occur in diabetes. A sensitive index for this is forced oscillation. It is a non invasive equivalent of dynamic lung compliance. It measures respiratory resistance during resting breathing and detects early inflammation in peripheral airway disease.

Impaired lung function can cause diabetes mellitus. Patients with reduced lung function are at increased risk of developing insulin resistance and hyperinsulinemia. Impaired lung function that is decrease in FVC and FEV1 can be risk factors for glucose intolerance, resistance to insulin and type2 diabetes mellitus. This may be due to effect of hypoxemia in glucose and insulin regulation and also due to inflammatory mediators in lung and its effect of signalling on insulin.

Various pulmonary functions like airflows and lung volumes, respiratory muscle strength, ventilation & perfusion relationship, diffusion and gas exchange in diabetes can be measured by spirometry, body plethysmography, nitrogen wash out, carbon monoxide diffusing capacity DLCO measurements in diabetics.

Spirometry in diabetes

Spirometer was invented by John Hutchinson to measure what he called vital capacity that is capacity to live. Since then it has become an important aspect of evaluation of respiratory disease. It assess lung volumes and airflows during inspiration and expiration. So it is a simple expression of a complex process just like measuring blood pressure.

There are several studies suggesting that pulmonary dysfunction may be one of the earliest measurable non metabolic alteration in diabetes. Mastubara & Hara et al (40) studies on pulmonary function and changes in microscopic structure of lungs in diabetics show significant decrease in Forced vital capacity, total lung capacity, residual volume in diabetics compared to control group.

Makkar P et al (36) also showed various changes in pulmonary function in the form of decline in FVC, peak expiratory flow, mid expiratory flow 75% in diabetes.

Mckeever et al showed that decrease in FEV1, FVC is associated with increase in HbA1c levels. Singh et al (1995) found

significant reduction in forced vital capacity in diabetes but no change in FEV1, PEFr.

Asanuma et al (16), Lange et al, Boulber et al have reported that FVC, FEV1 are reduced in diabetes compared to controls. Rosenecker et al showed decline in pulmonary function in diabetes over a 5 year period. Davis et al (38) also reported decline in FVC,FEV1 in diabetics.

Indications of spirometry in diabetes

- Mandatory lung function monitoring in diabetics every two years
- Diabetic patients with history of cough, unexplained dyspnoea, chest pain ,wheezing, smoking history
- Diabetics with abnormal chest x-ray, arterial blood gas values
- Screening of lung function in those diabetics with abnormal blood sugar and HbA1c levels.
- Preoperative risk assessment in diabetics

Contraindications of spirometry in diabetics

- Hemoptysis.
- dizziness, headache, nausea, vomiting.
- recent upper abdominal, thoracic surgeries.
- recent history of eye surgeries, glaucoma.
- recent history of severe chest pain, unstable angina, myocardial infarction
- thoracic aneurysm, pneumothorax.

Spirometry can be done by flow sensing or volume displacement

Spirometers.

American thoracic society recommends that equipment should be such that

- it can be calibrated with a 3 litre syringe
- it should record atleast FEV1 and FVC
- It should record a flow volume curve or loop

Spirometry manoeuvre

Expiratory manoeuvre -done by taking a full deep breath from the spirometer and then holding the mouth piece between lips to create a good seal, patient has to expire hard and fast as possible until no breath is left.

Expiratory and inspiratory manoeuvre-breathe in and out for 2-3 tidal breaths, then expire as fast as possible until no breath is left. Patient has to inspire rapidly to maximum capacity. Patient should be encouraged continuously to ensure best effort.

Acceptable tests-

Effort should be maximum, smooth and cough free.

Exhalation time should be atleast 6 seconds

Reproducibility as indicated by FVC should be within 5% or 100ml between highest and next best test among three acceptable tests. Best value among three is selected.

Spirometry



DLCO in diabetes

Diffusing capacity of lungs is estimated using carbon monoxide. CO has similar physical properties to oxygen in terms of its solubility and ability to diffuse across membranes. It will be strongly bound to haemoglobin so that all CO transferred across alveolar wall is retained within circulation and not exhaled.

Diffusion across the capillaries and alveolar gas exchange is affected in diabetes due to alveolar capillary basement membrane thickening. This is evidenced by decrease in DLCO in diabetes. DLCO is affected by amount of blood in lung capillaries. So DLCO

can be used as a simple non invasive method to estimate pulmonary capillary damage in diabetes.

Mori et al (15) showed decreased carbon monoxide diffusion capacity in diabetics as duration of diabetes increases. Asanuma et al (16) also showed negative correlation between DLCO and diabetes duration. Schuyler et al showed decreased DLCO in younger Type 1 diabetics. Schernthaner et al (5) in contrast showed no significant impairment in DLCO in diabetes.

DLCO can be measured by single breath or steady state methods. These methods are based on fick's law of diffusion.

Glycosylated haemoglobin and pulmonary function

HbA1C serves as an index of glycemic control over a period of 4 weeks to 3 months. There are several studies showing increased HbA1C values associated with decline in lung function in diabetics. Every 1% increase in HbA1C can cause 4% decline in FVC. Moris et al (15) studies in contrast showed no relationship between HbA1C and pulmonary function. 2010 American Diabetes Association has fixed HbA1c levels $> 48\text{mmol/mol}$ or $\geq 6.5\%$ as another criteria for diagnosis of diabetes.

Techniques to measure HbA1C include

- High performance liquid chromatography
- Immunoassay
- Enzymatic assay
- Capillary electrophoresis

Duration of diabetes and pulmonary function

Due to an increase in the duration of diabetes mellitus (DM), thickening of the capillary basal membrane, increase in capillary permeability, blood flow and viscosity and disturbances in the functions of platelets may be observed in diabetics, particularly in the ones who are genetically susceptible. Schuyler described significant decline in transpulmonary pressure at 50 and 60% of total lung capacity (TLC) and decreased TLC type I diabetes patients. He concluded that the observed decreases in lung recoil pressure at these lung volumes were due to premature aging of lung elastic elements as a result of longer duration of diabetes. Mori showed that DLCO% was decreased significantly with increase in duration of diabetes and the reduction was greater in patients with diabetic microangiopathy (especially nephropathy) and in those on insulin treatment. Other Pulmonary function tests showed no relationship. Sandler et al

concluded that 60% of a diabetic population had abnormal pulmonary function, mild reduction of lung elastic recoil and/or a reduction in pulmonary capillary blood volume. The degree of pulmonary dysfunction was correlated with the duration of DM.

MATERIALS AND METHODS

TYPE OF STUDY

This is an Observational study done to evaluate the various pulmonary manifestations in type2 diabetes mellitus patients.

STUDY PERIOD

The study was done during a period of 8 months from march 2012 to October 2012.

STUDY POPULATION

150 Type 2 diabetes patients

STUDY CENTRE

The study was done at the Department of Thoracic medicine and Department of Diabetology, Madras medical college& Rajiv Gandhi Government General Hospital, Chennai.

Proforma was designed, Ethical committee clearance was obtained. The nature and purpose of study was explained in detail to the study population. Written informed consent was obtained from all patients included in the study.

INCLUSION CRITERIA:

All patients with age more than 30 years with proven Type 2 diabetes mellitus with or without respiratory symptoms/signs were included in the study.

EXCLUSION CRITERIA:

- Known case of any obstructive or restrictive lung diseases
- Smokers
- Other immune compromised state or malignancy
- Known heart disease, Chronic kidney disease, Liver disease
- Patients not giving consent for the study
- Patient too ill to participate in the study

STUDY PROCEDURE

Patients with proven diabetes mellitus with or without respiratory symptoms fulfilling the inclusion criteria were included in the study. The following investigations were done in all the study population

1. CBC
2. FBS, PPBS, HbA1C

3. Chest X-Ray

4. Mantoux test

5. ECG

6. ECHO

For those with respiratory symptoms

7. Sputum AFB

8. Sputum gram stain

9. Sputum C&S

10. Fungal smear and culture

Glycemic control was assessed by fasting blood sugar, post prandial blood sugar and HbA1c values. HbA1C was measured by high performance liquid chromatography technique.

After ruling out active infection, pulmonary function test in the form of spirometry was done. Spirometry was also done in an equal number of age and sex matched control population.

Spirometry was performed using a computerised easy one spirometer. Patient was made to sit, asked to wear a nose clip and

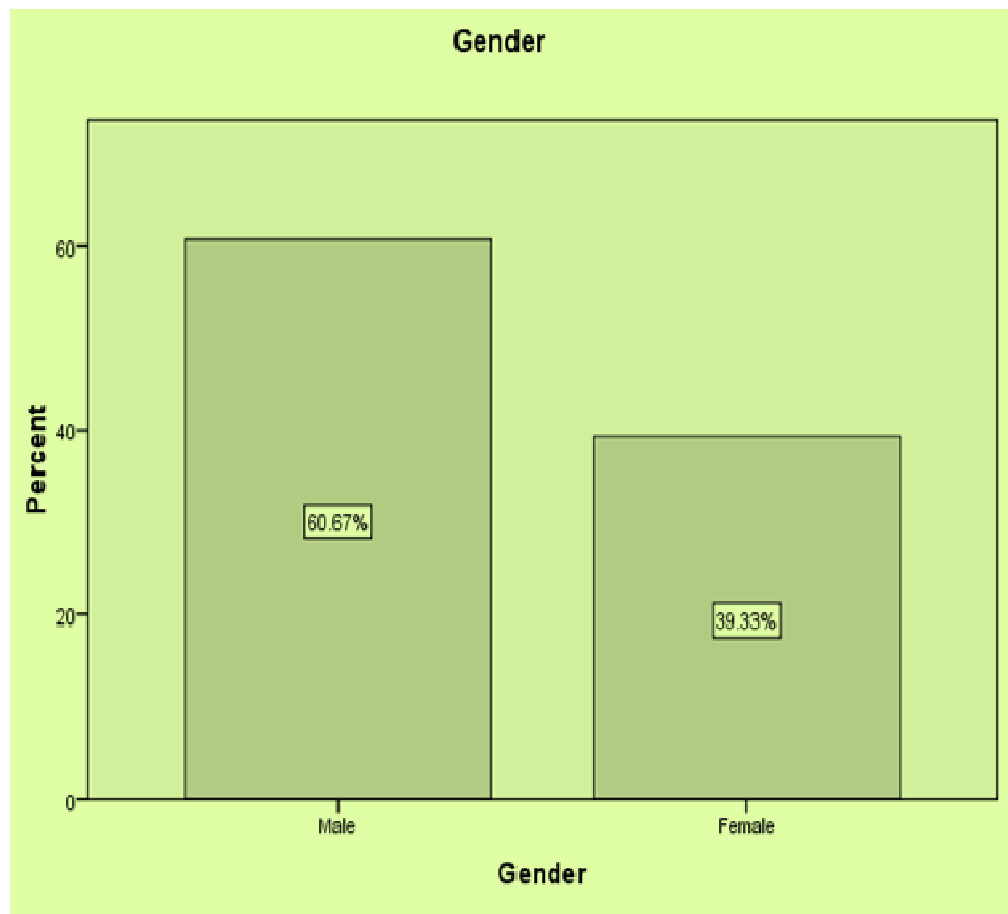
spirometry was performed according to American Thoracic Society recommendation. FVC or forced vital capacity, FEV1 or forced expiratory volume in 1st second, FEV1/FVC ratio or Forced expiratory ratio also known as FEV1% ,forced expiratory flow between 25 & 75 % of FVC ,peak expiratory flow rate were measured. All these values of pulmonary function were compared with values in age and sex matched control population. Pulmonary function values were correlated with the duration of diabetes and level of glycemic control.

HRCT, Bronchoscopy and other investigations were done wherever indicated.

RESULTS

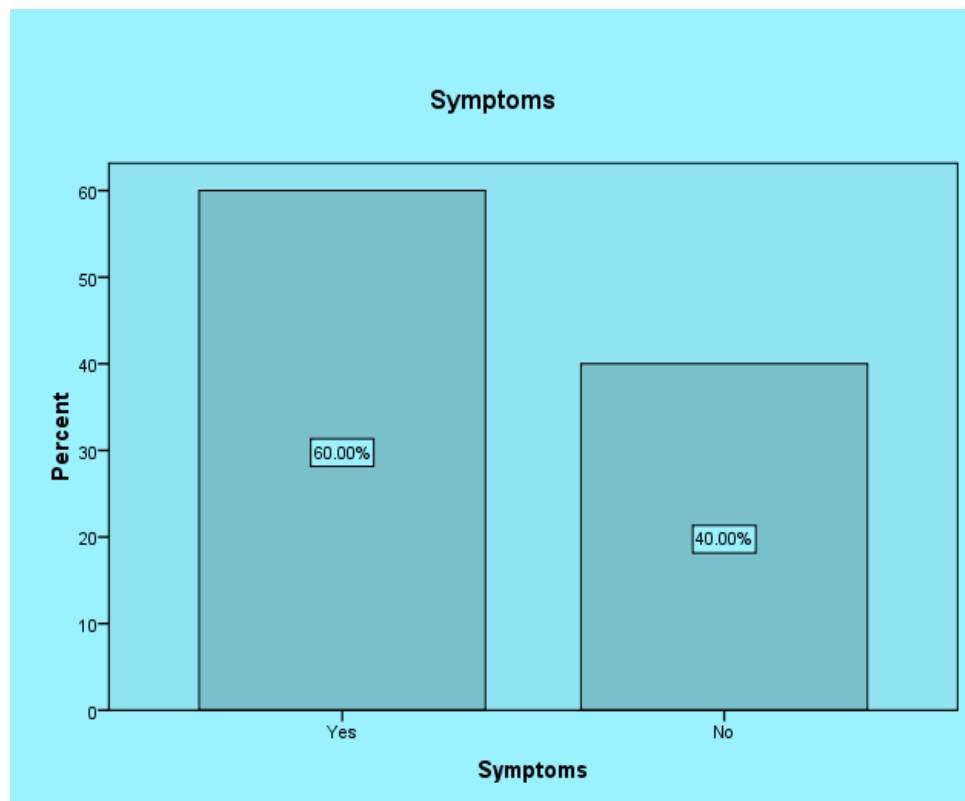
Of the 150 patients in the study group 91 were males and 59 were females. 60% of the study group were symptomatic, of which 37.3% were males & 22.7% were females. Of the symptomatics (n=90), 50% had pulmonary tuberculosis, 33.3% had other bacterial and fungal infections, 16.6% had no active infection, 60% mantoux negative & 40% were mantoux positive. Of the pulmonary TB patients 71.1% were sputum positive & 28.8% were sputum negative. 65.6% of sputum positive were mantoux positive. Radiologically most common finding in pulmonary TB was lower lung field TB. Klebsiella pneumonia was the most common bacterial infection other than TB. Pulmonary function tests were done in 60 asymptomatics & 15 symptomatics without active infection and 75 age and sex matched control population.

Of the 150 patients in the study population 60.67% were males and 39.33% were females

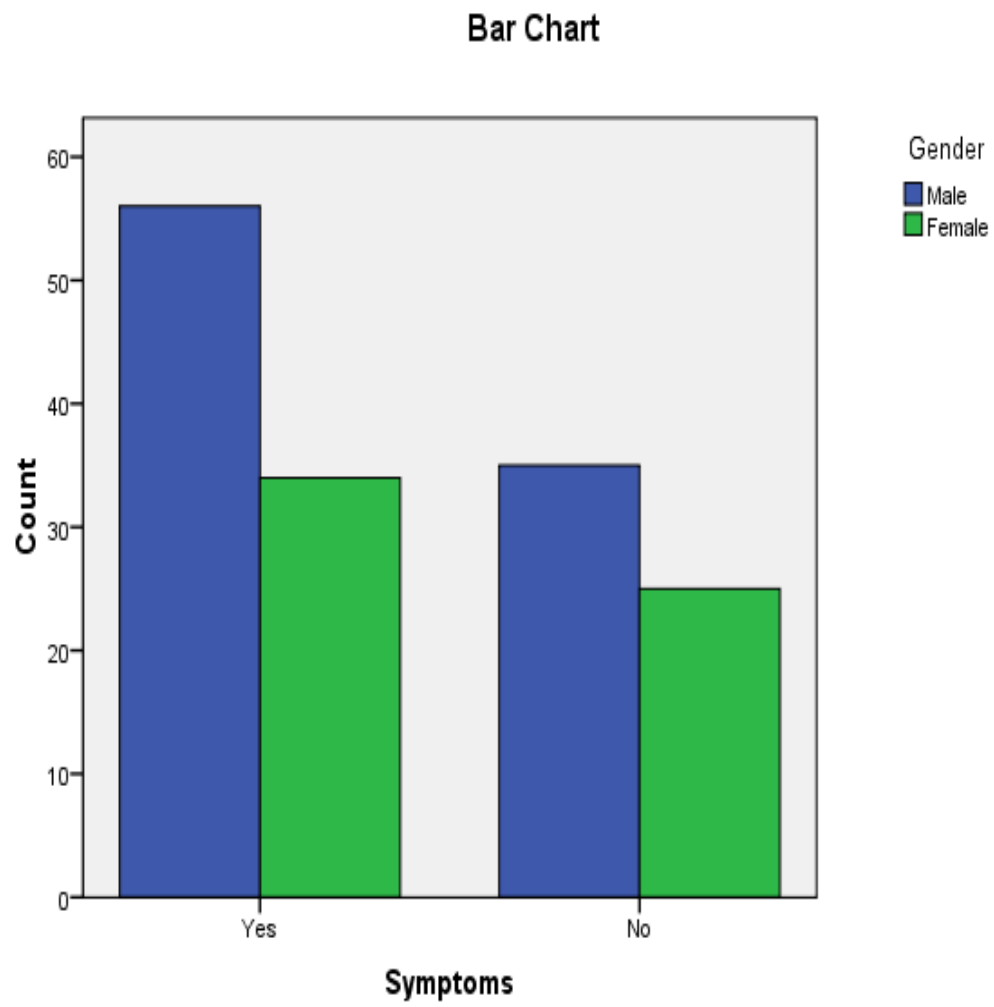


60% of the study population had respiratory symptoms and 40% were without symptoms.

		Frequency	Percent	Valid Percent
Valid	Yes	90	60.0	60.0
	No	60	40.0	40.0
	Total	150	100.0	100.0



			Gender		
			Male	Female	Total
Symptoms	Yes		56	34	90
		% of Total	37.3%	22.7%	60.0%
	No	Count	35	25	60
		% of Total	23.3%	16.7%	40.0%
Total		Count	91	59	150
		% of Total	60.7%	39.3%	100.0%



37.3% of males and 22.7 % of females were symptomatic.

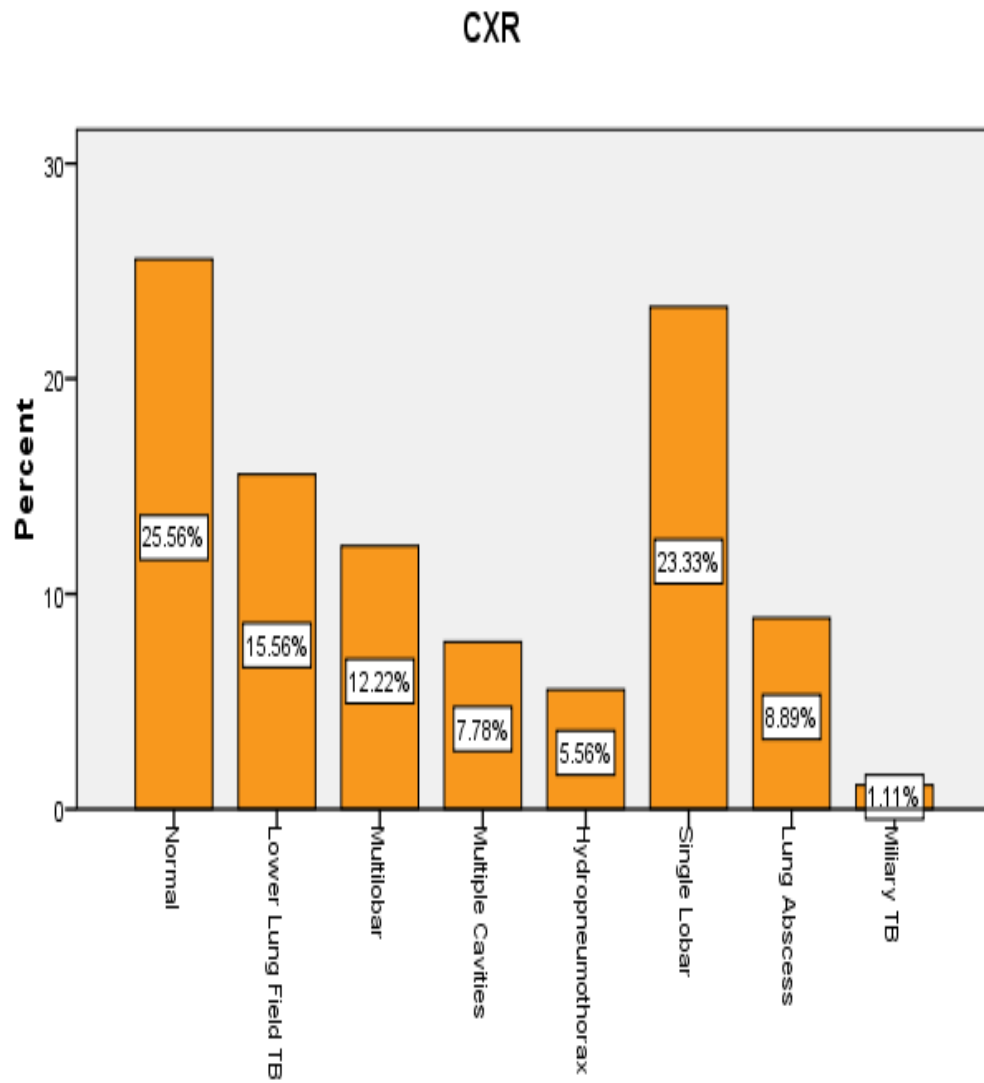
Of the 90 symptomatics , 25.6% had normal chest x-ray, 15.6% had lower lung field tuberculosis,12.2% had multilobar involvement,23.3% had single lobar involvement.

CXR FINDINGS IN THE SYMPTOMATICS

	Frequency	Percent
Normal	23	25.6
Lower Lung Field TB	14	15.6
Multilobar	11	12.2
Multiple Cavities	7	7.8
Hydropneumothorax	5	5.6
Single Lobar	21	23.3
Lung Abscess	8	8.9
Miliary TB	1	1.1
Total	90	100

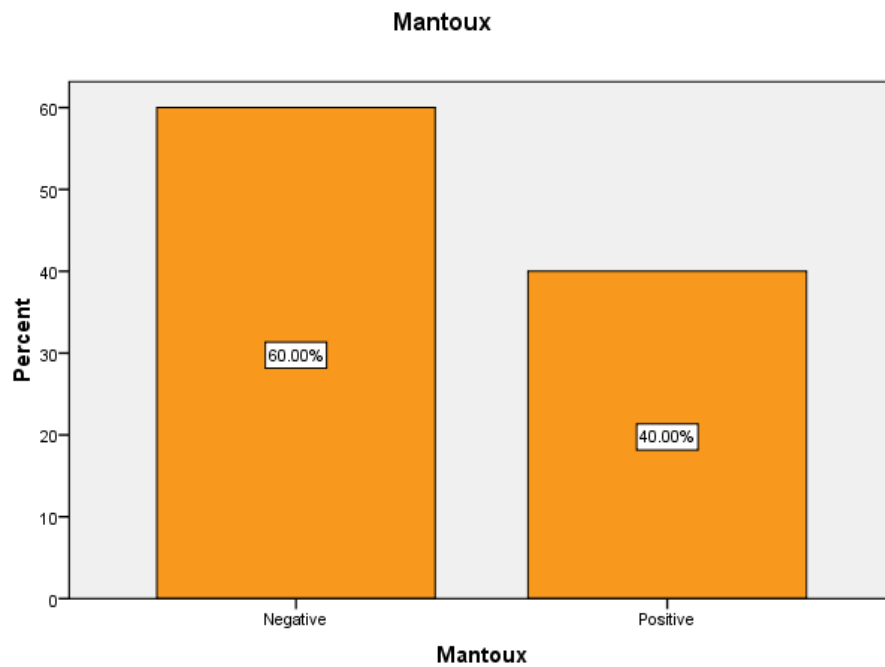
7.8% had multiple cavities in the chest x-ray, 8.9% had lung

abscess, 1.1% had miliary shadows and 5.6% had hydropneumothorax



MANTOUX TEST RESULTS

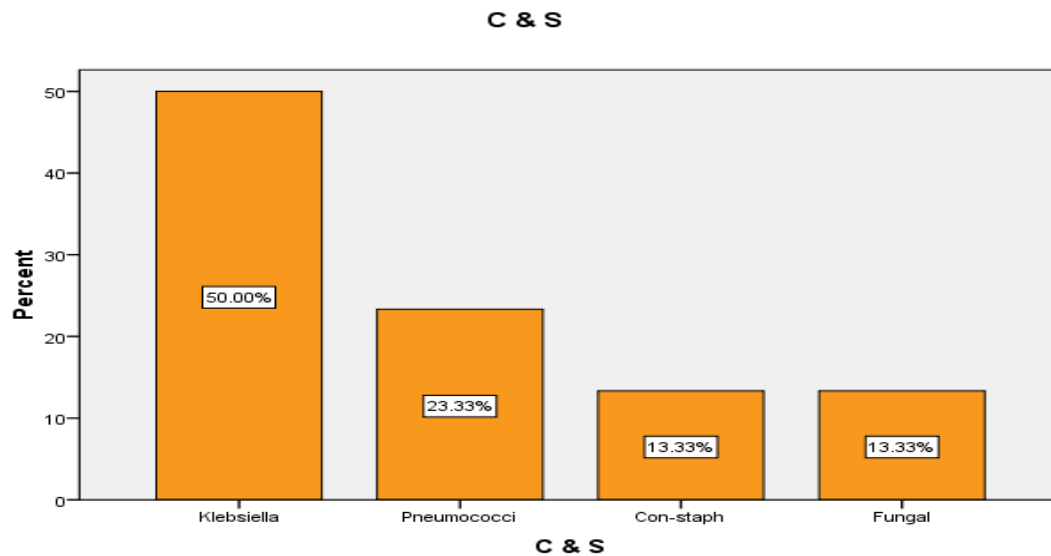
		Frequency	Percent
Valid	Negative	54	60.0
	Positive	36	40.0
	Total	90	100.0



Of the 90 symptomatics mantoux test was positive in 60% and negative in 40%.

Of the 90 symptomatics, 30 had bacterial infections other than tuberculosis, 45 had pulmonary tuberculosis, 15 had normal chest xray and no growth of any organisms in sputum.

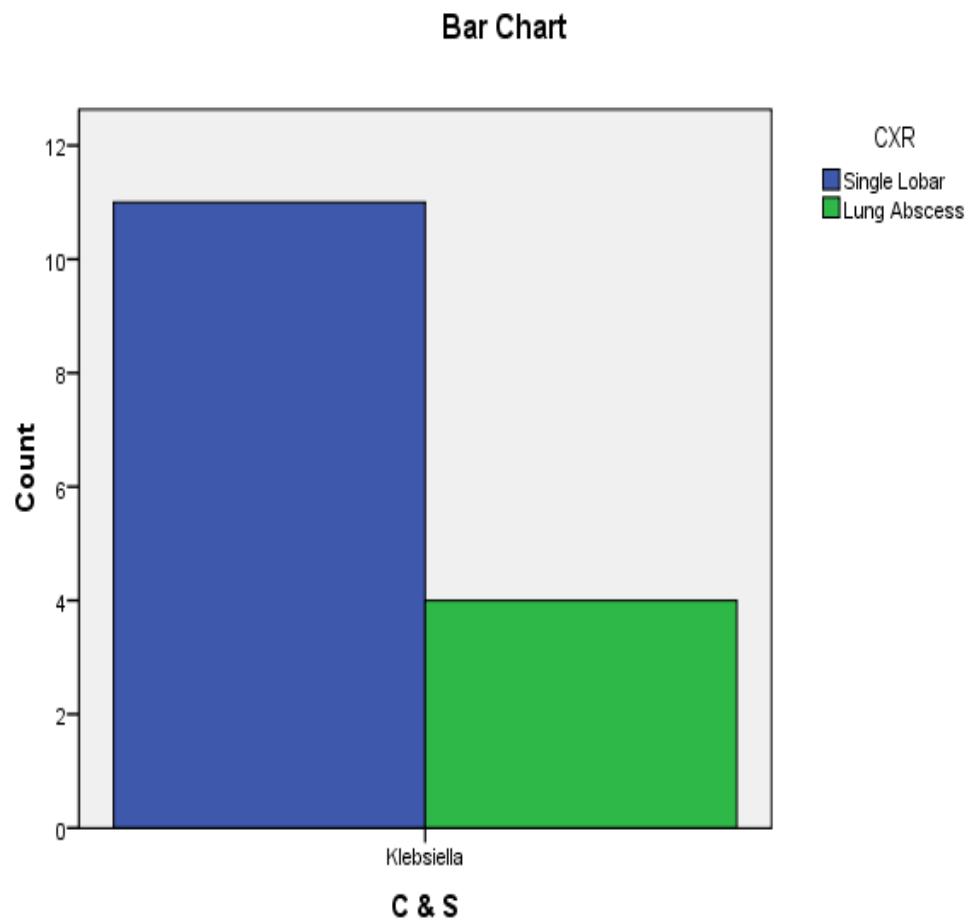
Sputum C&S		Frequency	Valid Percent
	Klebsiella	15	50.0
	Pneumococci	7	23.3
	Con-staph	4	13.3
	Fungal	4	13.3
	Total	30	100.0



Of the bacterial infections, 50% had klebsiella pneumonia, 23.33% had pneumococcal infections, 13.33% had coagulase negative staphylococci infections and another 13.33% had fungal infections. 26.66% of patients with bacterial infections had normal chest x ray and were treated as acute bronchitis, remaining had multilobar, single lobar involvement, lung abscess etc.

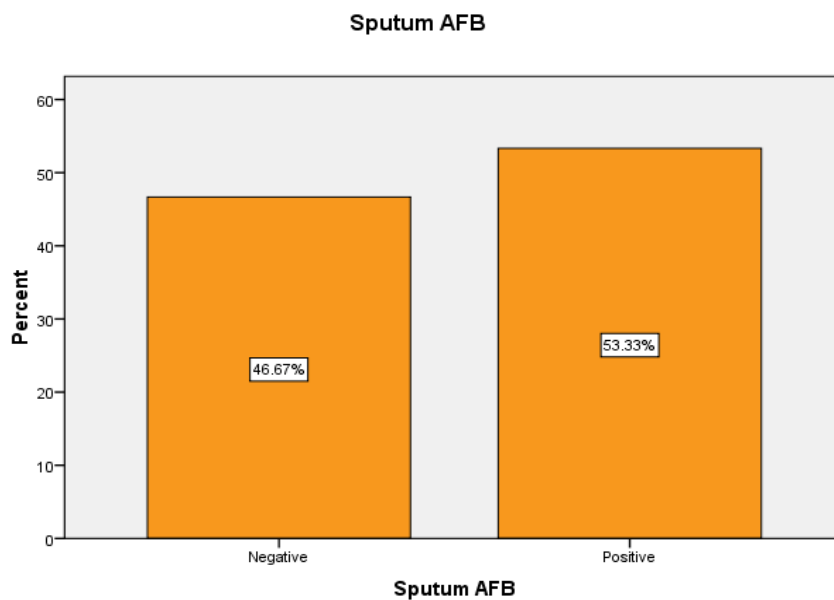
		CXR		
		Single Lobar	Lung Abscess	Total
Klebsiella		11	4	15
	% of Total	73.3%	26.7%	100.0%
Total	Count	11	4	15
	% of Total	73.3%	26.7%	100.0%

Out of 15 Klebsiella Pneumonia infections, 11 patients presented with single lobar pneumonia.(In this 6 cases were Right upper lobe pneumonia) and 4 patients presented as lung abscess.



SPUTUM AFB RESULTS

	Frequency	Percent	Valid Percent
Negative	28	31.1	46.7
Positive	32	35.6	53.3
Total	60	66.7	100.0
System	30	33.3	
Total	90	100.0	



Excluding 30 cases of bacterial infections out of the 90 symptomatics, sputum for AFB was positive in 53.3% and negative in 46.7%.

Out of 90 symptomatics, 45 cases were diagnosed as pulmonary tuberculosis based on chest xray, sputum AFB and mantoux reports.

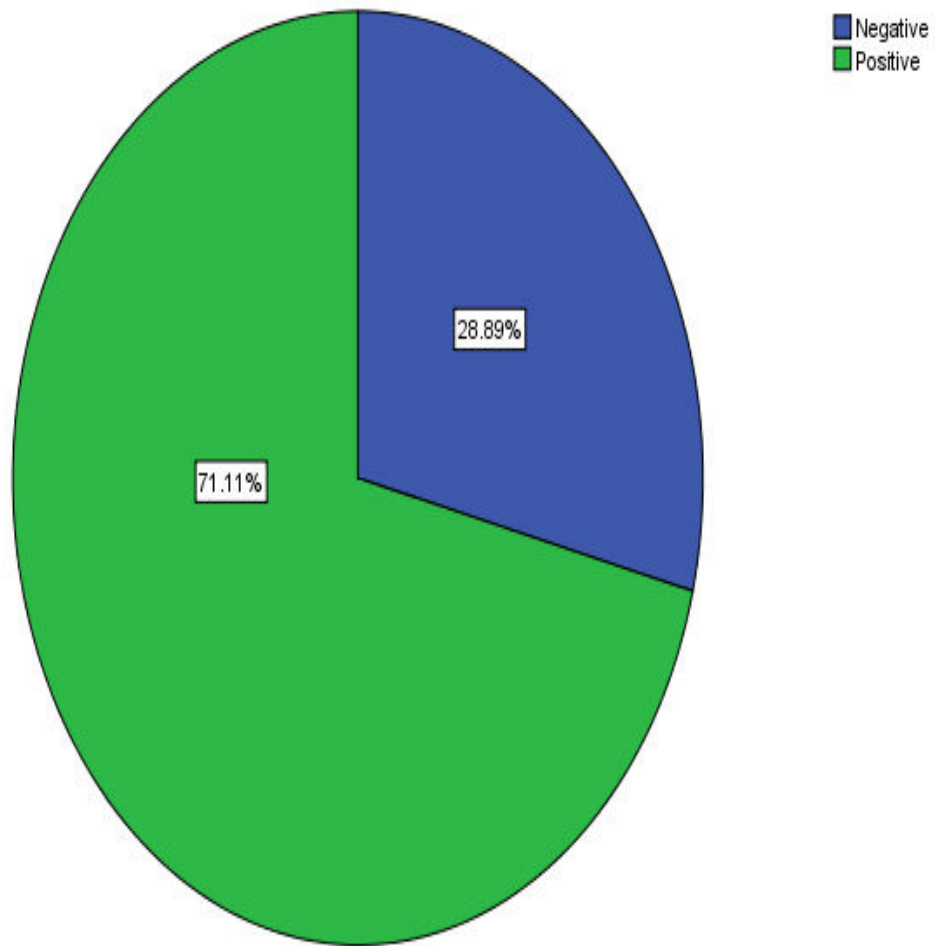
Of the 45 TB cases 71.1% were sputum positive and 28.9% were sputum negative.

SPUTUM AFB & PULMONARY TB

		Frequency	Percent
Valid	Negative	13	28.9
	Positive	32	71.1
	Total	45	100.0

65.6% of sputum positive pulmonary tuberculosis were mantoux positive.

Sputum AFB



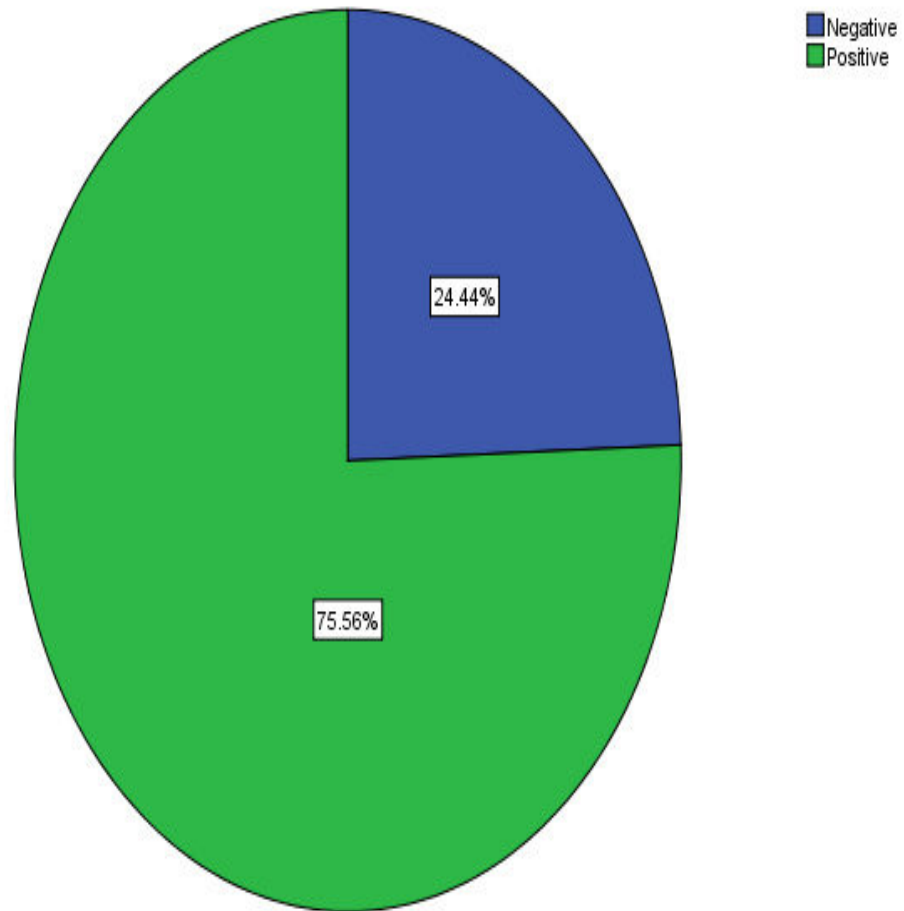
MANTOUX AND PULMONARY TB

		Frequency	Percent
Valid	Negative	11	24.4
	Positive	34	75.6
	Total	45	100.0

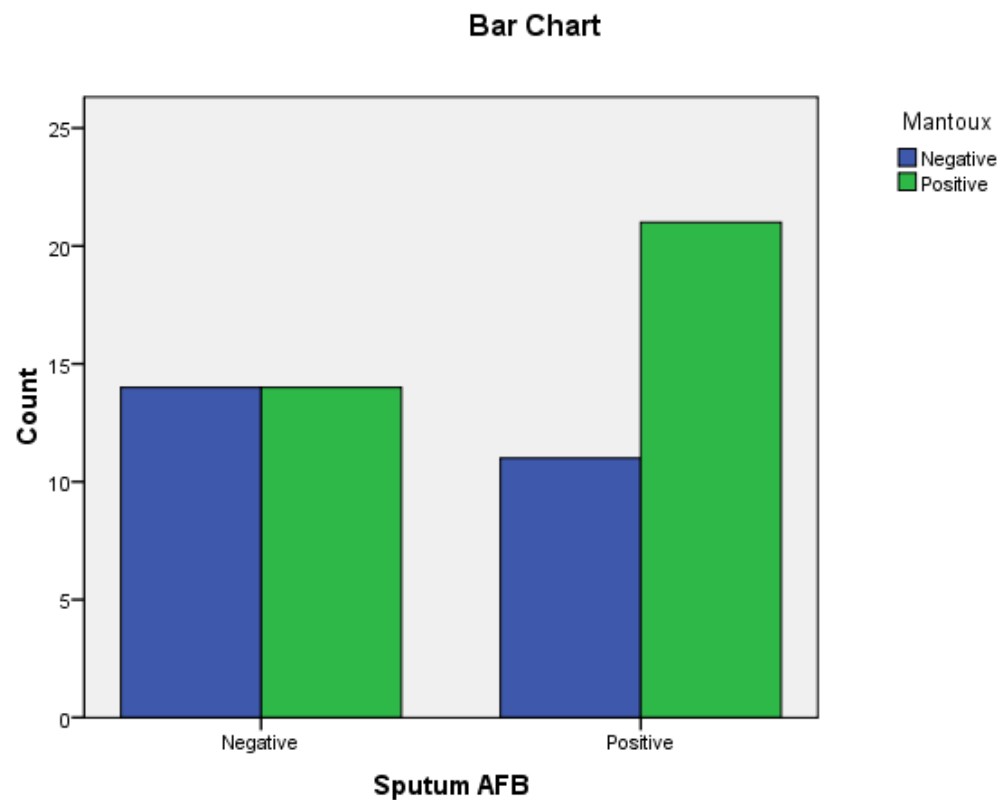
75.6% of pulmonary TB cases were mantoux positive and 24.4%

were mantoux negative.

Mantoux



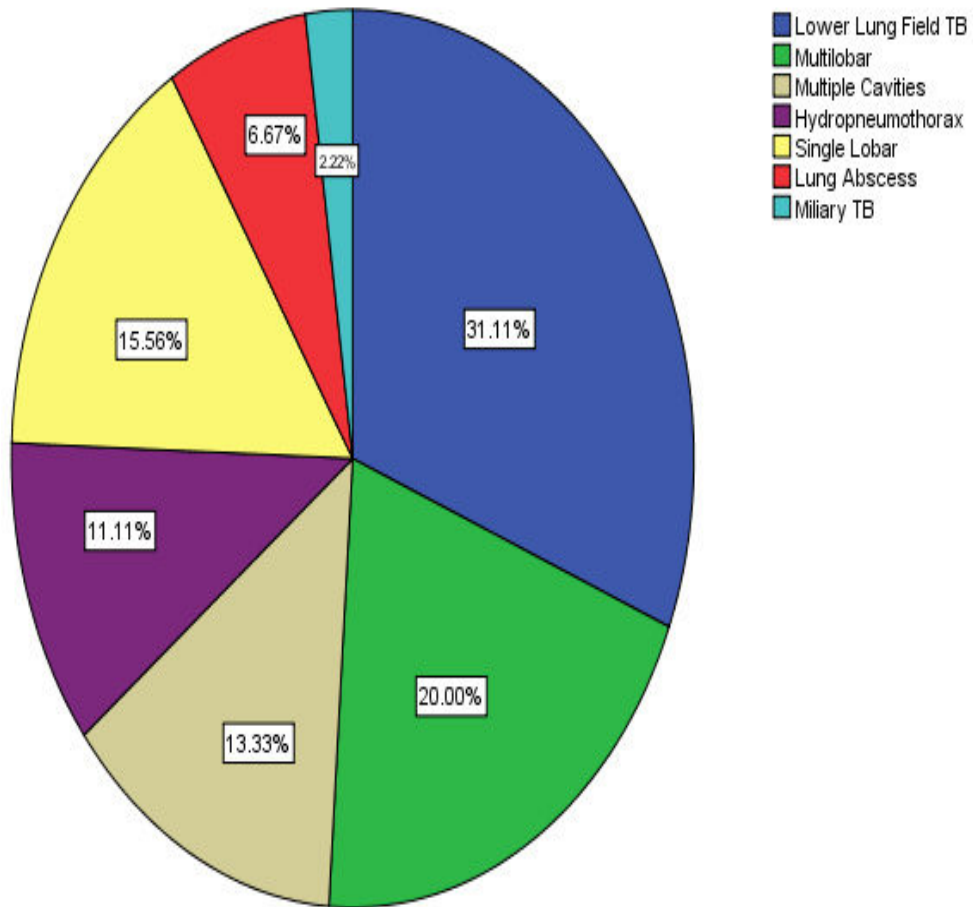
Of the 32 sputum positive pulmonary TB cases ,21 cases were mantoux positive and 11 cases were mantoux negative. The remaining 13 sputum negative pulmonary TB cases were diagnosed on the basis of mantoux positivity and chest xray findings.



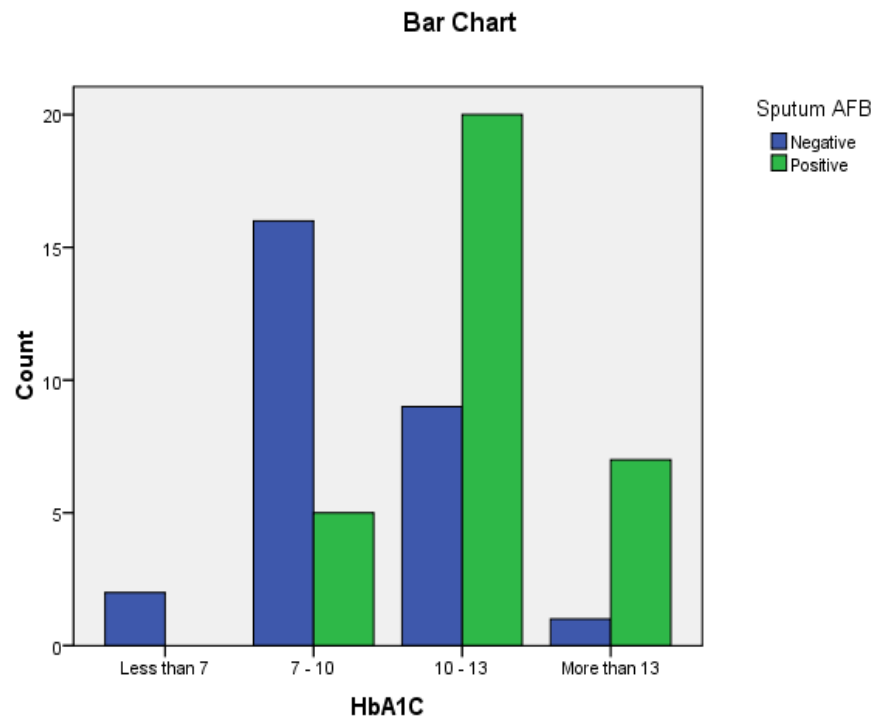
	CXR PATTERN IN PULMONARY TB	Frequency	Percent
Valid	Lower Lung Field TB	14	31.1
	Multilobar	9	20.0
	Multiple Cavities	6	13.3
	Hydropneumothorax	5	11.1
	Single Lobar	7	15.6
	Lung Abscess	3	6.7
	Miliary TB	1	2.2
	Total	45	100.0

Of the various radiological manifestations of pulmonary TB, most common was lower lung field TB .31.11% had lower lung field TB, 20% had multilobar ,15.56% had single lobar involvement,13.3 % had multiple cavities,11.11% had hydropneumothorax,6.67 % had multiple cavities and 2.2% had miliary TB.

CXR

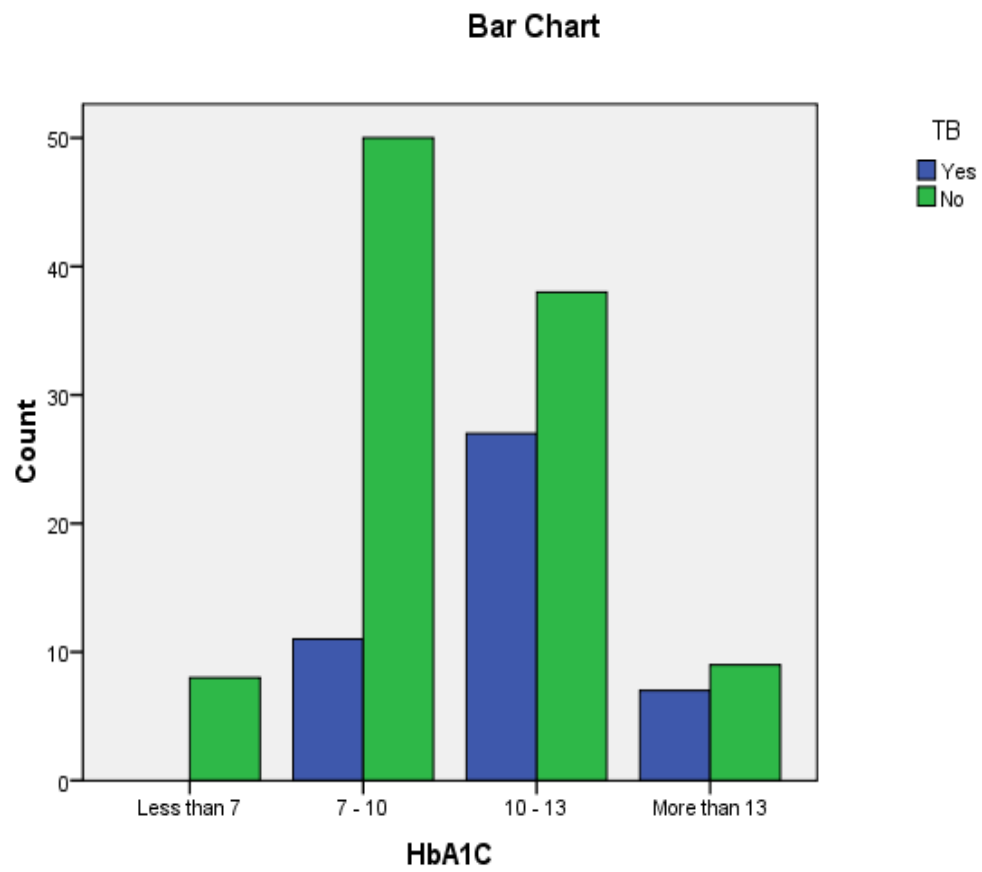


Maximum sputum positivity among pulmonary TB cases were found with HbA1C in the range between 10-13 and no sputum positive cases were found in those with good glycemic control (HbA1C <7).



PULMONARY TB & HbA1C LEVELS

HbA1C			Yes	No	Total
HbA1C	Less than 7	Count	0	8	8
		% of Total	.0%	5.3%	5.3%
	7 - 10	Count	11	50	61
		% of Total	7.3%	33.3%	40.7%
	10 - 13	Count	27	38	65
		% of Total	18.0%	25.3%	43.3%
	More than 13	Count	7	9	16
		% of Total	4.7%	6.0%	10.7%
	Total	Count	45	105	150
		% of Total	30.0%	70.0%	100.0%



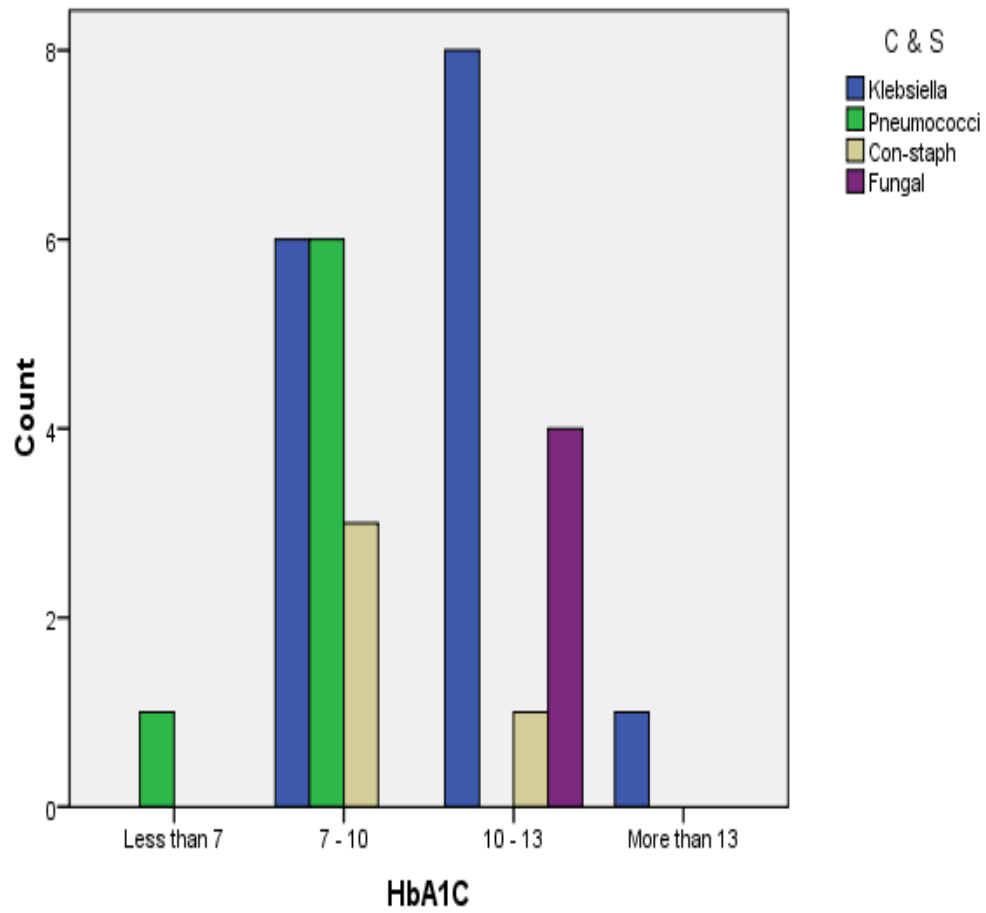
PULMONARY TB AND HbA1C LEVELS

HbA1 C	BACTERIAL INFECTIONS				Total
Less than 7	Klebsiella	Pneumococci	Con-staph	Fungal	
	0 (0%)	1 (3.3%)	0 (0%)	0 (0%)	1 (3.3%)
7 -10	6 (20%)	6 (20%)	3 (10%)	0 (0%)	15 (50%)
10- 13	8 (26.7%)	0 (0%)	1 (3.3%)	4 (13.3%)	13 (43.3%)
More than 13	1 (3.3%)	0 (0%)	0 (0%)	0 (0%)	1 (3.3%)
Total	15 (50%)	7 (23.3%)	4 (13.3%)	4 (13.3%)	30 (100%)

Bacterial infections were also more common in the HbA1C range

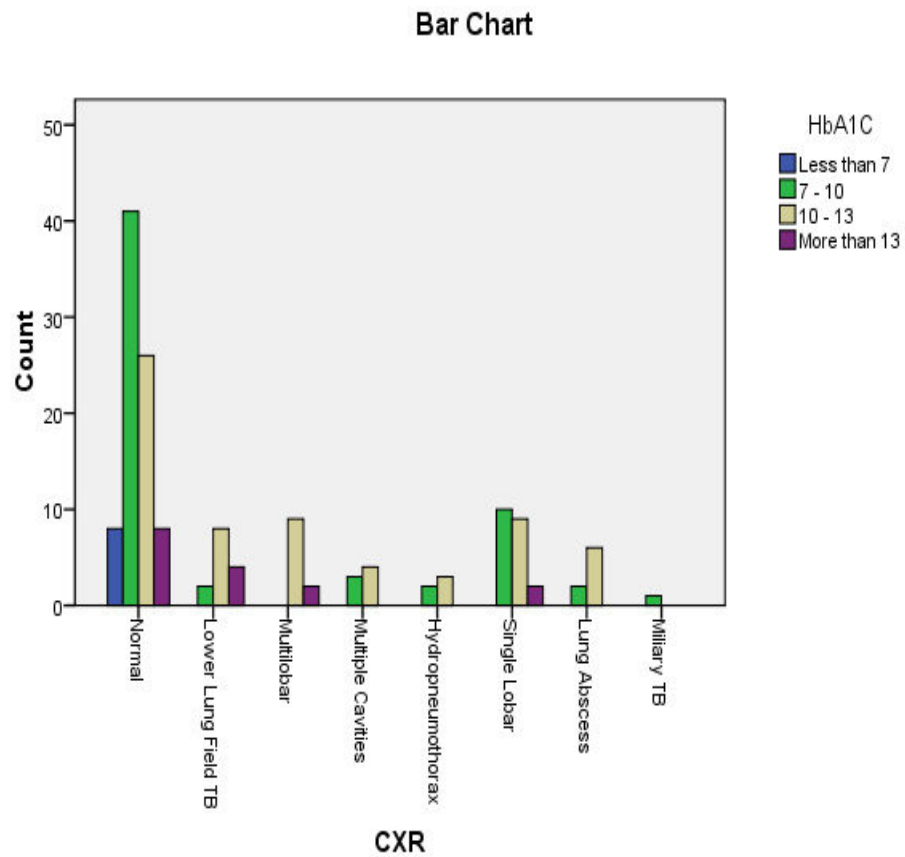
between 10-13, of which klebsiella was most common.

Bar Chart



Radiographic manifestations of pulmonary TB and bacterial

infections were also more prominent in the HbA1C range of 10-13

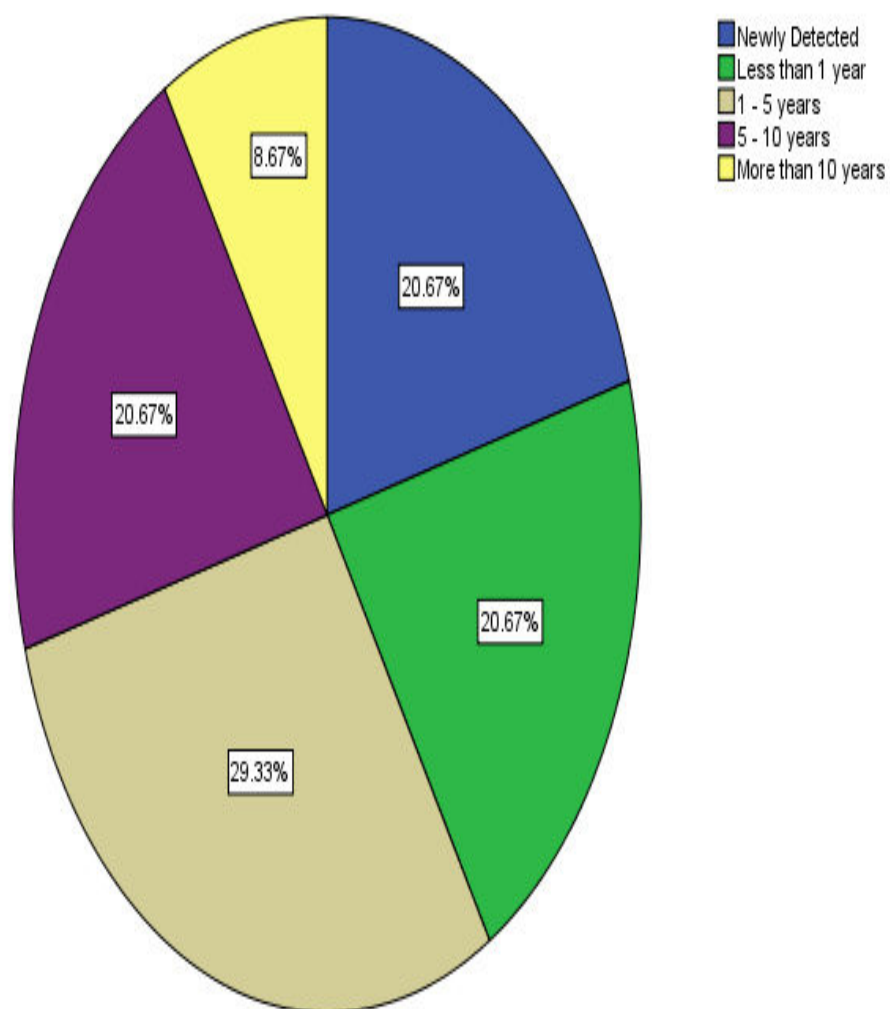


DURATION OF DIABETES IN THE STUDY POPULATION

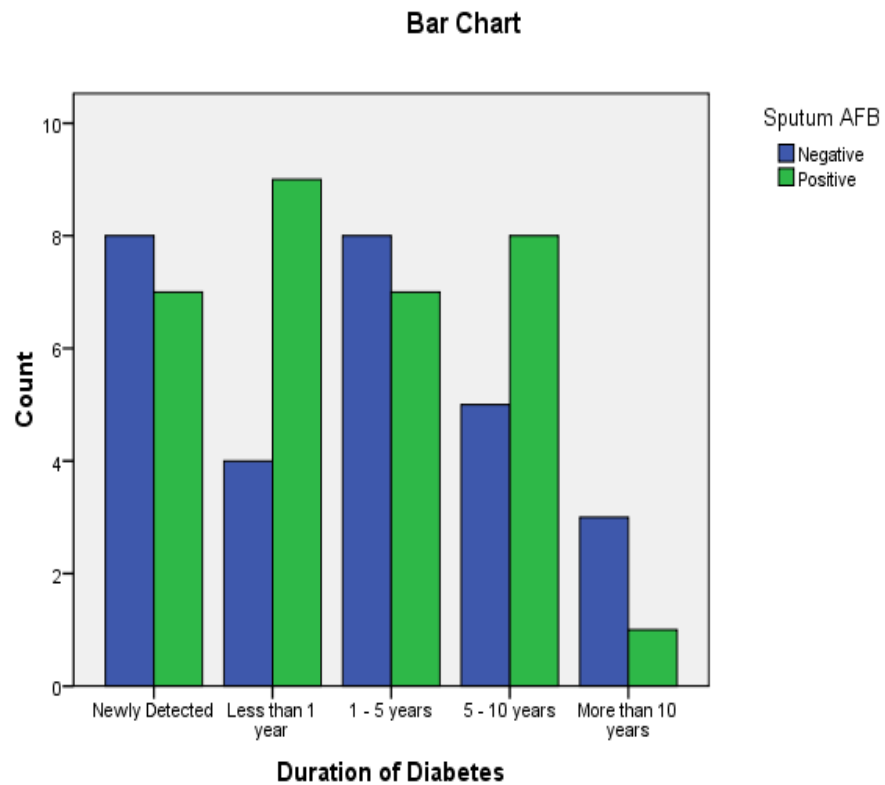
		Frequency	Percent
Valid	Newly Detected	31	20.7
	Less than 1 year	31	20.7
	1 - 5 years	44	29.3
	5 - 10 years	31	20.7
	More than 10 years	13	8.7
	Total	150	100.0

Maximum number of cases were in the 1-5 year group

Duration of Diabetes



RELATION BETWEEN SPUTUM AFB POSITIVITY AND DIABETES DURATION

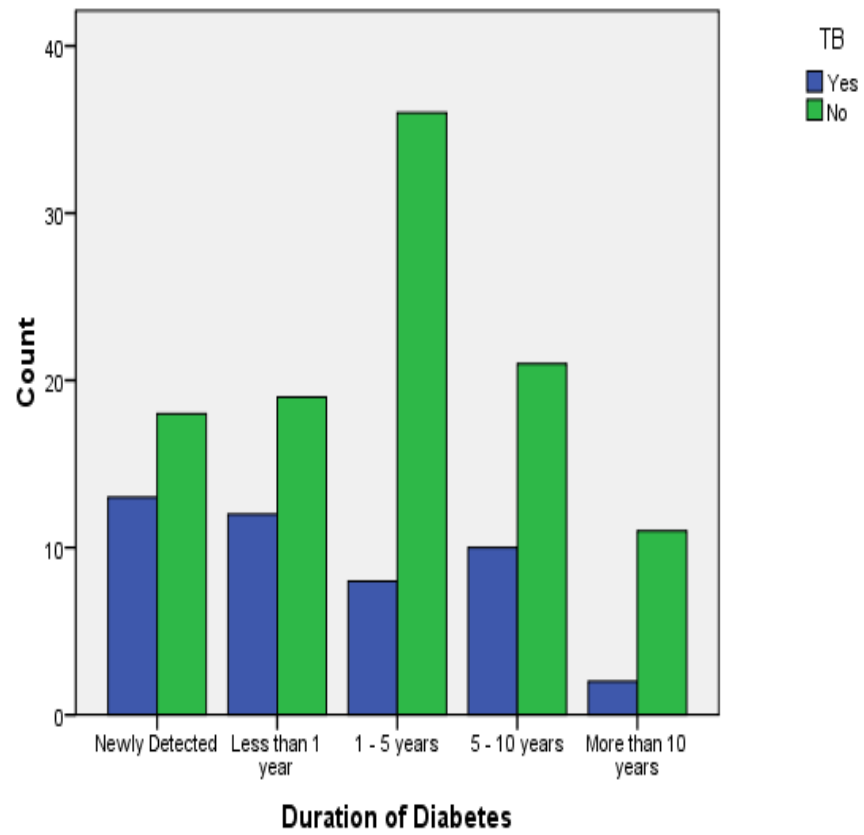


Maximum number of sputum positive cases were seen in duration of diabetes less than 1 year.

PULMONARY TB AND DURATION OF DIABETES

			TB		
Duration of Diabetes	Newly Detected	Count	13	18	31
	Less than 1 year	% of Total	8.7%	12.0%	20.7%
		Count	12	19	31
	1 - 5 years	% of Total	8.0%	12.7%	20.7%
		Count	8	36	44
		% of Total	5.3%	24.0%	29.3%
	5 - 10 years	Count	10	21	31
		% of Total	6.7%	14.0%	20.7%
	More than 10 years	Count	2	11	13
		% of Total	1.3%	7.3%	8.7%
	Total	Count	45	105	150
		% of Total	30.0%	70.0%	100.0%

Bar Chart



RESULTS OF PULMONARY FUNCTION TEST

CORRELATION BETWEEN PULMONARY FUNCTION TEST AND DURATION OF DIABETES

		PULMONARY FUNCTION TEST	Duration of Diabetes
	FEV1	Correlation Coefficient	-.464**
		Sig. (2-tailed)	.000
		N	75
	FVC	Correlation Coefficient	-.370**
		Sig. (2-tailed)	.001
		N	75
	FEV1 / FVC	Correlation Coefficient	-.331**
		Sig. (2-tailed)	.004
		N	75

CORRELATION BETWEEN PULMONARY FUNCTION TEST
AND HbA1C LEVELS

	PULMONARY FUNCTION TEST	HbA1C
FEV1	Correlation Coefficient	.000
	Sig. (2-tailed)	.996
	N	75
FVC	Correlation Coefficient	.008
	Sig. (2-tailed)	.946
	N	75
FEV1 / FVC	Correlation Coefficient	.112
	Sig. (2-tailed)	.340
	N	75

COMPARISON BETWEEN FEV1 IN DIABETIC PATIENTS AND
NON DIABETIC CONTROLS

		FEV1	FEV1 - Control
FEV1	Pearson Correlation	1	.802**
	Sig. (2-tailed)		.000
	N	75	75
FEV1 - Control	Pearson Correlation	.802**	1
	Sig. (2-tailed)	.000	
	N	75	75

Forced expiratory volume in the 1st second FEV1 shows statistically significant decrease in diabetic patients compared to non diabetic controls (pvalue<0.01)

COMPARISON OF FVC BETWEEN PATIENTS AND CONTROLS

		FVC	FVC - Control
FVC	Pearson Correlation	1	.697**
	Sig. (2-tailed)		.000
	N	75	75
FVC - Control	Pearson Correlation	.697**	1
	Sig. (2-tailed)	.000	
	N	75	75

** . Correlation is significant at the 0.01 level (2-tailed).

Forced vital capacity also shows reduction that is statistically significant in patients compared to controls

COMPARISON OF FEV1/FVC BETWEEN DIABETIC PATIENTS
AND NON DIABETIC CONTROLS

FEV1 / FVC	Pearson Correlation	1	.267*
	Sig. (2-tailed)		.021
	N	75	75
FEV1 / FVC - Control	Pearson Correlation	.267*	1
	Sig. (2-tailed)	.021	
	N	75	75

Correlation is significant at the 0.05 level (2-tailed).

DISCUSSION

This study was mainly done to assess the pulmonary manifestations including pulmonary functions in type 2 diabetes mellitus. Main emphasis was given on pulmonary function in asymptomatic diabetics and symptomatics without active infection. This was then compared with non-diabetic age and sex match control population.

Duration of diabetes in the study group ranged from 1 month to 30 years. Glycosylated haemoglobin was done in all patients to assess the glycemic control, since many studies showed that poor glycemic control had an adverse effect on lung function. FEV1 values were lower in diabetics compared to non diabetic controls with a p value<0.05 .These findings were similar to that of Asanuma et al (16), SanjeevSinha et al(27),Lange et al studies. This decrease may be due to alveolar epithelium and capillary endothelium, basement membrane thickening and decreased elastic recoil of the lung.

Forced vital capacity values also showed statistically significant reduction in diabetics than non diabetic controls. Similar findings were observed in Makkar P et al(36), McKeer et al , Sanjeev et al,Maurizio(8) et al studies. This reduction in FVC may be due to glycated proteins in connective tissue that decrease the elastic recoil of the lung as well as pulmonary microangiopathy.

All the spirometric parameters showed significant reduction correlating with the duration of diabetes. Since HbA1c levels reflects glycemic control over a period of only 3 months, no significant correlation was found between pulmonary functions and HbA1C. This finding was against Davis et al(38) studies that showed decreased lung function associated with poor glycemic control.

Several studies also demonstrated decrease in PEF due to decreased capacity of respiratory muscles, decreased FEF 25-75% and also decrease in maximum voluntary

ventilation (MVV) due to decreased respiratory muscle endurance.

Among infections in diabetes mellitus , pulmonary TB was most common. Most common radiological pattern in pulmonary TB was lower lung field involvement. This was similar to the results of the largest study done about radiological manifestations in TB-PerenzGusman(24) et al study, which showed increased lower lung field lesions. Multiple cavities were another common presentations in diabetics.

Several studies showed that risk of developing sputum positive pulmonary TB is five times higher in diabetics. Of the 45 pulmonary TB patients ,32 were sputum positive in the study group. Diabetes cause immune suppression that results in high bacillary load in TB patients with diabetes.

Bacterial infections are also more common in diabetics and associated with higher mortality. Most common bacterial pathogen other than TB causing disease in the study group was *Klebsiella pneumoniae*.

CONCLUSION

- Pulmonary function tests FEV1 and FVC are reduced in diabetics, compared to non diabetic control population.
- Reduction in FEV1 And FVC correlates with the duration of diabetes, but not with HbA1C levels.
- Lung involvement in asymptomatic diabetics can be assessed by pulmonary function test.
- Diabetics are more susceptible to pulmonary tuberculosis, recurrent pneumonia associated with higher mortality rates, fungal infections due to alteration in host defence, respiratory epithelium function and cilia motility.
- Most common bacterial infection in diabetes was pulmonary tuberculosis followed by klebsiella pneumonia infection
- Elevated blood glucose levels negatively affect the outcome in pneumonia as well as other infections. The importance of optimal glycemic control and its effect on the respiratory system can be assessed,thus the adverse

outcome on the lung due to uncontrolled diabetes can be reduced.

- As the prevalence of type 2 diabetes reaches epidemic proportions, the pathophysiology of lung involvement in diabetes assumes greater relevance.
- In future we can extend the study by including DLCO, respiratory pressures, non volatile tests in a large sample group for more accurate assessment of pulmonary function in diabetics.

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INFORMATION SHEET

- We are conducting an observational study on “Evaluation of pulmonary manifestations in Type2 Diabetes mellitus and correlation between pulmonary function tests and glycemictcontrol” at Department of Thoracic Medicine, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai.
- The purpose of the study is to evaluate the various clinical and radiological pulmonary manifestations in diabetes mellitus and to study the correlation between pulmonary function in diabetic patients based on PFT values and glycemict control assessed by FBS , PPBS, HbA1C.
- The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.
- Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time; your decision will not result in any loss or benefits to which you are otherwise entitled.
- The results of the special study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment.

Signature of investigator

Signature of participant

Date:

PATIENT CONSENT FORM

Study Details :“Evaluation Of Clinic oradiological Pulmonary Manifestations In Type 2 Diabetes Mellitus and Correlation Between Pulmonary Function Test and Glycemic Control” at Madras Medical College and Rajiv Gandhi Government General Hospital ,Chennai.

Study Centre : Department of Thoracic Medicine and Diabetology, Madras Medical College, Chennai.

Patient may check(✓) these boxes

I confirm that I understood the purpose of procedure for the above study.Ihave the opportunity at ask question and all my questions and doubts have been answered to my complete satisfaction.

I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected.

I understand that the sponsor of the clinical study, others working on the sponsor’s behalf, the ethical committee and the regulatory authorities will not need my permission to look at my health records, both in respect of current study and any further research that may be conducted in relation to it, even if I withdraw from my study I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published , unless as required under the law. I agree not to restrict the use of any data or results that arise from this study.

I agree to take part in the above study and comply with the instructions given during the study and faithfully cooperate with the study team and to immediately inform the study staff if I suffer from any deterioration in my health or wellbeing or any unexpected or unusual symptoms.

I hereby give permission to undergo complete clinical examination and diagnostic tests including haematological, biochemical, radiological and pulmonary function test. I hereby consent to participate in the study.

Signature/Thumb impression

Patient name and address:

Signature of investigator:

Date: Place:

Study Investigator’s name :

Date :

PROFORMA

Name of the patient:

Age :

Sex:

Date:

Presenting Complaints:

Duration of diabetes :

Type of Diabetes : Type 1 / Type II

On: OHA / Insulin

Past H/o Respiratory Disease: Yes / No

Past H/o heart disease:

Smoker:

Investigations:

CBC: Hb PCV TC

DC RBC ESR

RFT:B.Urea S.Creatinine

LFT:S.Bilirubin

SGOT:

SGPT:

T.Protein:

FBS :

PPBS:

HbA1C :

Mantoux

Sputum AFB:

Sputum C/S

Sputum Fungal Smear:

Echo/ ECG:

CXR :

PFT :

HRCT:

Bronchoscopy :



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